UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/890,363	11/02/2001	David Laurence Becker	HO-P02246US0	1593

26271 7590 07/22/2005

FULBRIGHT & JAWORSKI, LLP
1301 MCKINNEY
SUITE 5100
HOUSTON, TX 77010-3095

EXAMINER	
MCGARRY, SEAN	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 07/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/890,363	BECKER ET AL.	
	Examiner	Art Unit	
	Sean R. McGarry	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-30 and 43-79* is/are pending in the application.

4a) Of the above claim(s) *27-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-26,43-61 and 65-79* is/are rejected.

7)☒ Claim(s) *62-64* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 16-26 and 43-61, and 65-79 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification discloses SEQ ID NO: 12 which corresponds to the cDNA encoding the human species of protein connexin 43. The specification also discloses 3 specific antisense oligonucleotide sequences for connexin 43 (it appears that there is one for chick (SEQ ID NO: 3), one for mouse(SEQ ID NO: 2) and one for human(SEQ ID NO: 1)) and one for each of connexin 26, 31.1, and 32 (it is not clear from the specification what species these are targeted to). Methods using antisense targeted to SEQ ID NO: 12 and methods using SEQ ID NOS: 1, 2, and 3 meet the written description provisions of 35 USC 112, first paragraph. However, the claims are directed to encompass gene sequences, sequences that hybridize to SEQ ID NO: 12 , corresponding sequences from other species, mutated sequences, allelic variants, splice variants, sequences that have a recited degree of identity (similarity, homology), and so forth. The invention reads on any sequence that may be a connexin 43. The scope includes a vast number of potential targets. The invention includes antisense that may target 1, 2, 3, or more different connexins (see page 10). There are no species of antisense disclosed that target 2 or more different connexins. The antisense for use

in the claimed methods are not required to have absolute complementarity but, may have some level of noncomplementarity that is not clearly defined by structure (see page 9, for example). It is not clear what species the antisense oligonucleotides described as SEQ ID NOS: 4-6 target since the specification fails to provide such a description. Effective antisense sequences cannot be predicted and must be found by a trial and error process. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In *re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel* , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that

it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the example does, does not necessarily describe the cDNA itself. No sequence information indicating which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5.

The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Claims 16-26, 43-61, and 65-79 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods using the local

administration of the specific connexin 43 antisense oligonucleotides exemplified and methods using antisense targeted to nucleic acid encoding connexin 43 which corresponds to SEQ ID NO: 12, does not reasonably provide enablement for the full scope embraced in the instant claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant invention is drawn to method of treatment of various conditions such as reducing neuronal death resulting from neuronal insult, promoting wound healing, and reducing inflammation or scarring as part of a wound treatment. The claimed invention is so broad as to encompass the treatment of any condition that may be associated with connexin expression (including mutant, or up regulated expression, or down regulated expression, or etc., of any nucleic acid that encodes any protein that may be considered a connexin protein where the different connexin proteins have different structures and functions where the different connexins are differentially expressed in different cells and/or tissues at different times and where the expression of the different connexins may or may not be related to any particular stimulus/stimuli. The invention is drawn to the use of antisense oligonucleotides that are targeted to any connexin 43 gene sequence, sequences that hybridize to SEQ ID NO: 12, corresponding sequences from other species, mutated sequences, allelic variants, splice variants, sequences that have a recited degree of identity (similarity, homology), and so forth. The scope includes a vast number of potential targets. The scope of treatments embraced by the instant claims is limited only by some association with

connexin 43, where the condition would require down regulation of connexin expression (this includes mutants, for example). The invention includes antisense that may target 1, 2, 3, or more different connexins (see page 10). There are no species of antisense disclosed that target 2 or more different connexins. The antisense also for use in the claimed methods are not required to have absolute complementarity but, may have some level of noncomplementarity that is not clearly defined by structure (see page 9, for example). It is not clear what species the antisense oligonucleotides described as SEQ ID NOS: 4-6 target since the specification fails to provide such a description. Effective antisense sequences cannot be predicted and must be found by a trial and error process.

The specification provides several examples using specific antisense oligonucleotides targeted to connexin 43 via a local administration where there was shown a correlation in the inhibition of connexin 43 and improved wound healing, inhibition of inflammation associated with wounds, and neuronal cell death inhibition.

The specification does not provide any specific guidance for any other connexin 43 other than the specific oligos and the disclosure of SEQ ID NO: 12. There is no specific guidance for any other connexin in the treatment of any condition other than the statements that antisense to connexins can be used in the treatment of a condition that would require inhibition of such connexins where no specific guidance on what specific conditions might be treatable by any particular antisense to any particular connexin, for example.

The art of antisense therapy is an unpredictable art, which requires specific guidance for the treatment of any particular disease. Branch [TIBS Vol. 23, February 1998] addresses the unpredictability and the problems faced in the antisense art with the following statements: "[a]ntisense molecules and ribozymes capture the imagination with their promise or rational drug design and exquisite specificity. [h]owever, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "[t]o minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. [t]his is a challenging quest."; "[h]owever, their unpredictability confounds research applications of nucleic acid reagents."; "[n]on-antisense effects are not the only impediments to rational antisense drug design. [t]he internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,. . ."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. [a]ntisense compounds are no exception. [a]s is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve and therapeutic index is known."; [c]ompared to the dose response curves of conventional drugs, which typically

span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "[b]ecause it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "[b]inding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. [s]ince accessibility cannot be predicted, rational design of antisense molecules is not possible."; and, "[t]he relationship between accessibility to ODN binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored. . . [i]t is not yet clear whether *in vitro* screening techniques. . . will identify ODNs that are effective *in vivo*."

It is noted that the instant specification provides guidance for connexin 43 and has shown a correlation between antisense inhibition of connexin 43, but has failed to provide such a disclosure or a disclosure that would show by correlation for the use of antisense oligonucleotides targeted to the vast scope of connexin targets in the treatment of disease.

Jen et al [STEM CELLS Vol. 18:307-319, 2000] discuss antisense based therapy and the challenges that remain before the use of antisense becomes routine in a therapeutic setting. Jen et al discuss the advances made in the art but also indicate that progress needs to be made in the art. In the conclusion of their review Jen et al assert "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also stated "[t]he key challenges to this field have been outlined above. [I]t is clear that they will have to

be solved if this approach to specific antitumor therapy is to become a useful treatment approach. [a] large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." It is clear from Jen et al that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome.

It is noted that the instantly claimed invention is not necessarily limited to the local administration of antisense oligonucleotides but also reads on parenteral, intramuscular, intravenous, etc., administration of antisense oligonucleotides. It is clear from the cited art that sufficient delivery of antisense to the targeted cells or tissues is an obstacle in the at of nucleic acid therapies.

Agrawal [TIBTECH, Vol. 14:376-387, October 1996] states the following: " [t]here are two crucial parameters in drug design: the first is the identification of an appropriate target in the disease process, and the second is finding an appropriate molecule that has specific recognition and affinity for the target, thereby interfering the disease process" (page376); "[o]ligonucleotide must be taken up by cells in order to be effective. [s]everal reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is a complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum . . .[i]t is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency." (Page 378); "[m]icroinjection or using

lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is nt clear how relevant this approach is for *in vivo* situations." (Page379); "[a]ny antisense activity observed in such artificial systems [cell culture] should be scrutinized carefully with respect to the disease process and its applicability to *in vivo* situations." (Page 379).

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Qui et al and Hodins (both cited on form 892) speak to the use of antisense directed to connexin 43 for the treatment of wounds and inflammation and resulting scar tissue. Both are published subsequent to the instant filing.

Claim 50 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. It is noted that the claims from which claim 50 depend from require antisense to connexin 43. The context of claim 50 provides the choice of two connexin targets that do not appear to require that one be connexin 43.

Claim 70 is objected to because of the following informalities: It appears that the term "tissue" was inadvertently left out of claim 70 after the word "said" claim 70. Appropriate correction is required.

Applicant's arguments filed 5/12/05 have been fully considered but they are not persuasive. Applicant response is directed to the amending of the claims to connexin 43. It is noted that the Official Action of record indicated that the specific antisense molecules disclosed and antisense oligonucleotides targeted to SEQ ID NO: 12 were described and method of using them were enabled. The claims rejected are not so limited and the claims are rejected for the reasons set forth above. It is noted that arguments/evidence that connexin 43 sequences have been well characterized and known in the prior art would be given weight in consideration of arguments for the grounds of rejection under written description.

Claims 62-64 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R. McGarry whose telephone number is (571) 272-0761. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sean R McGarry
Primary Examiner
Art Unit 1635